Remarks

As a preliminary matter, attention is directed to the extension of time (three months) enclosed herewith.

Claims 1-15, 18-44, 47-72, 75-92, 95-102, 104-112, 115-122, 124-132, 135-145, and 156-161 are currently pending.

Claims 3-11, 19-24, 32-40, 48-53, 60-68, 76-81, 88-91, 96-101, 108-111, 116-121, 128-131, and 136-141 have been withdrawn from consideration.

Claims 16-17, 45-46, 73-74, 93-94, 103, 113-114, 123, 133-134, and 146-155 were previously canceled.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-145, and 156-161 are currently under examination, all having been rejected.

General Comments

References to the Office Action of May 30, 2007 include reference to the Paragraph numbers provided by the Examiner. References to Applicants' specification include reference to bracketed paragraph numbers in the application published as US 2002/0006443 A1.

Each of independent claims 1, 30, 58, 86, 106, and 126 has been amended to state that the solubility-improved form is selected from a crystalline highly soluble salt form, a high-energy crystalline form, and an amorphous form. Support is in the specification at [0025], last 8 lines.

Each of independent claims 1, 30, 58, 86, 106, and 126 has also been amended to specify that the drug and polymer are combined as a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form. Support is in the specification at [0029], 16th-22nd lines.

New claim 164 has been added, is supported by claim 1, and is limited to a drug in a crystalline highly soluble salt form as the solubility-improved form and to HPMCAS as the concentration-enhancing polymer. No fee is thought to be due for adding the new claim since at least an equal number have been canceled previously. If, however, the Commissioner determines that any fee is due, please charge it to Deposit Account No. 16-1445. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

No new matter is believed to have been added. Entry of the amendments is accordingly respectfully requested.

Summary of the Rejections

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, and 142-145 continue to be rejected under 35 USC 102(b) over Miyajima, US 4,983,593.

Claims 1-2, 12-15, 18, 25-31, 41-44, 54-59, 69-72, 75, and 82-85 continue to be rejected under 35 USC 102(b) as being anticipated by Dunn, US 4,461,759.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 125-127, 132, 135 and 142-145 continue to be rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al., US 5,496,561.

Claims 1, 30, 58, 86, 126, and 156-161 continue to be rejected under §102(e) as anticipated by Bymaster, US 6,147,072.

Claims 87, 92, 95, 102, 105-107, 112, 115, 122, 124-127, 132, 135, and 142-145 continue to be rejected under §103(a) as obvious over Dunn.

Applicants continue to traverse the rejections for the reasons that follow.

The §102 rejections

1. As a preliminary matter in respect of the various anticipation rejections, Applicants submit that each of the references is legally insufficient to support an anticipation rejection. An anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims being rejected. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1349 (Fed. Cir. 1998). Under the authority of cases such as *In re Arkley*, 455 F.2d 586, 587-88 (CCPA 1972), it is impermissible to pick and choose among the hundreds of lines of text in a patent reference in order to arrive at the claimed subject matter. All of the references cited to support anticipation are missing one or more elements of the invention, as discussed below.

The §102 Rejection Over Miyajima

2. Miyajima does not anticipate because it does not disclose a solubility improved drug form within the scope of Applicants' claims. NZ-105, a hydrochloride salt, is excluded from the current claims by the following language which is reproduced from claim 1:

> wherein
> said composition is not a dispersion;
> said drug has an aqueous solubility less than about 1 mg/mL;
> **when said drug is basic, said solubility improved form has an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form;**

in which the emphasis by bolding has been supplied. By the above language, crystalline hydrochloride salts, including NZ-105, have been excluded from the claims. The quoted claim language requires the solubility-improved form to have an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline free base and the crystalline hydrochloride salt. Thus the more soluble of the crystalline hydrochloride salt (in Miyajima, efonidipine hydrochloride) and the crystalline free base is expressly excluded. The remaining form is also excluded because, being the less soluble of the two forms, it automatically lacks sufficient solubility to be within the scope of the claim.

3. The Examiner took the position that Applicants' definition of a "solubility-improved form" in paragraphs [0024], [0025], and [0026] would include NZ-105. See the office action, Paragraph 4, particularly the paragraph bridging pages 3 and 4, plus the following two paragraphs on page 4. In the last sentence on page 4, the examiner concludes: "Thus, by the definition for 'solubility-improved form or [sic: of] a drug,' the NZ-105 of Miyajima meets the limitations of 'solubility-improved form of a drug." Applicants respectfully disagree. The metes and bounds of Applicants' invention are defined by the claims, and the claims exclude crystalline hydrochloride salts, as just discussed. To argue that NZ-105, efonidipine hydrochloride, is within the scope of Applicants' claims is to argue that efonidipine hydrochloride has a solubility at least 2-fold the solubility of itself, an absurdity. As a hydrochloride salt, NZ-105 has been excluded from the claims and for this reason alone, Miyajima does not anticipate.

4. Miyajima further fails as an anticipatory reference because Miyajima does not disclose a composition of HPMCAS and NZ-105 that is a physical mixture, much less a physical mixture in which NZ-105 and HPMCAS are mixed in particulate form. Applicants' claims

expressly require that the solubility-improved form and the polymer are combined as a simple physical mixture. Miyajima prepares his compositions by dissolving NZ-105 and HPMCAS in an organic solvent and removing the solvent by evaporation. See Miyajima at column 2, lines 37-40. Miyajima's solvent processing method would not produce a physical mixture as defined by Applicants, i.e., one in which the individual components retain the same individual physical properties that they exhibit in bulk. See US 2002/0006443 A1 at [0029]. As an analogy to Miyajima's solvent process in which HPMCAS and NZ-105 are dissolved in an organic solvent (see Miyajima at column 3, lines 55-60 and column 3, line 67 to column 4, line 1), consider a composition produced, for example, by dissolving equal amounts of granulated sugar and granulated table salt in water followed by distilling off the water. The resulting composition will not be one containing individual granules of sugar and salt that retain the same properties (e.g., taste) as bulk sugar and bulk salt.

5. For the above reasons, it is submitted that Applicants cannot be anticipated by Miyajima, and it is respectfully submitted that the rejection should be withdrawn.

The §102 Rejection Over Dunn

6. Dunn does not anticipate because, *inter alia*, it does not disclose a drug in a solubility-improved form within the scope of Applicants' claims. Applicants reasoning parallels the arguments offered above in respect of the §102(b) rejection over Miyajima. Attention is directed to the claim language quoted from claim 1 in Paragraph 2 above.

7. Both verapamil and verapamil hydrochloride are outside the scope of Applicants' claims by virtue of the fact that neither has "an aqueous solubility at least 2-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form". Verapamil is the free base and verapamil hydrochloride is the hydrochloride salt. The language quoted above excludes the more soluble drug form whether it is the hydrochloride salt or the free base. The remaining form is automatically excluded by reason of being the less soluble of the two forms and, therefore, of possessing a solubility that is too low for it to be within the scope of Applicants' claims. Thus both verapamil and verapamil hydrochloride, i.e., the hydrochloride salt and the free base, are unequivocally excluded.

8. Verapamil and verapamil hydrochloride are the only species disclosed in Dunn within the scope of the phrase "verapamil or a pharmaceutically acceptable salt thereof". No other verapamil species is disclosed. Applicants respectfully submit that the phrase "or a pharmaceutically acceptable salt thereof" in Dunn's specification is not a disclosure of a

solubility-improved form, including those specifically identified in Applicants' claims, within the meaning of §102. The only pharmaceutically acceptable salt that Dunn discloses is verapamil hydrochloride. Dunn discloses nothing else that would constitute a solubility improved form physically mixed with a cellulosic ionizable concentration-enhancing polymer also required by Applicants' claims. Thus, the required element of a solubility-improved form is completely missing from Dunn.

The §102 rejection over Okada

9. Okada does not anticipate because it does not disclose a drug in a solubility-improved form physically mixed with a concentration-enhancing polymer within the scope of Applicants' claims.

10. The Examiner states in Paragraph 9:

> A mixture reads on mixing a polymer with the core materials in a fluidized bed to coat the core material containing the drug. Okada does not describe the formation of covalent or ionic bond between the drug and the polymer, such as bond formation would not be a physical process.

Applicants disagree on several grounds.

11. First, Okada does not disclose a physical mixture of one of his coating polymers with a drug, as implied by the Examiner. Okada merely describes coating a central core with an (enteric) polymer:

> As occasion demands, the central core composition may be coated with a water soluble high polymer, an acid soluble high polymer, an enteric high polymer, a water insoluble high polymer, wax or the like. (Okada, column 3, lines 36-39)

A polymer-coated core wherein the core contains a drug is not a physical mixture of the drug and the polymer as required by Applicants claims. The fluidized bed referred to by Okada (e.g., in the examples) is employed as a coating apparatus, and is in fact referred to as a "fluidized bed coating apparatus". See, for example, Okada's example 1 at column 6, line 27.

12. Second, the Examiner appears to be contending that chemical bonds between the drug and polymer must be formed in order to preclude the drug and polymer composition from qualifying as a physical mixture. Applicants respectfully disagree. Considering that an applicant is allowed to be his own lexicographer, a physical mixture is as Applicants defined it in their specification. Applicants defined a physical mixture of a drug and polymer to be, *inter alia*,

a composition of drug and polymer that has been physically mixed. That is, some form of mixing action is required to make a mixture. See US 2002/0006443 at [0029] where Applicants indicate that the individual components retain their bulk properties and that any conventional method may be used to mix the polymer and drug together. The dosage form disclosed in Okada, by contrast, is a structure, not a physical mixture. It comprises a polymeric membrane surrounding a central core containing drug, a structure in which no mixing of the surrounding membrane polymer(s) with the drug separately present in the core is involved. No embodiment is disclosed in Okada wherein a concentration enhancing polymer required by Applicants is physically mixed with a solubility-improved form of a drug, regardless of whether the polymer and drug are in particulate form.

13. With reference to the law as set forth in paragraph 1 above, in order to base an anticipation rejection on Okada one would need to select a particular polymer from among many polymers in Okada, home in on a particular drug in Okada, and then allege a physical mixture. But, Okada never describes or discloses a physical mixture of one of Applicants' cellulosic ionizable polymers and a solubility-improved drug form. The only disclosure in Okada of any polymer useful in Applicants' invention is in connection with making a membrane, not a physical mixture. The only disclosure of diclofenac sodium (noted by the Examiner in Paragraph 8) is in Example 9 where it is mixed with corn starch, not with one of the cellulosic ionizable concentration-enhancing polymers required by Applicants. The hydroxypropyl cellulose also mentioned in Example 9 is not one of Applicants' required polymers. Parenthetically, Applicants note that in their previous response it was inadvertently stated that hydroxypropyl cellulose was clearly employed by Okada as a membrane. Applicants wish to correct that statement in that it was intended to say it is believed Okada used hydroxypropyl cellulose as a binder.

14. To the extent Okada discloses any elements of Applicants' invention, they are disclosed in isolated and/or unrelated portions of the specification. Okada does not disclose the elements of the claimed invention arranged as in the claims being rejected. A §102 rejection cannot be based on Okada by selecting out isolated elements from the Okada specification and splicing them together, but with no direction in Okada to do so.

The §102 Rejection Over Bymaster

15. Bymaster does not anticipate because it does not disclose a physical mixture of a concentration-enhancing polymer and a solubility-improved form of a low-solubility drug.

16. The examiner commented as follows, in pertinent part:

> Bymaster discloses treating psychosis, acute mania, mild anxiety states or depression by administering to a patient in need thereof a composition that comprises a first component drug selected from olanzapine, clozapine, risperidone, sertindole, quetiapine and ziprasidone, and a second component (abstract; column 1, lines 42-46; column 2, line 9-51; and claim 2), and the composition is formulated as tablets, chewable tablets, capsules, solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions (column 10, lines 8-12) and polymers such as hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate are associated with the drug (column 10, lines 61-67).

In the above quotation the Examiner referred to column 10, lines 61-67 of Bymaster to support the rejection. Column 10, lines 61-67 is reproduced as follows:

> ...Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

17. The only occurrence in which a polymer required by Applicants' claims is coincidentally disclosed in Bymaster is as an enteric coating in the above text. A dosage form in which an enteric polymer is coated around a core is not a physical mixture, however. It is a structure in which drug and polymer are separated. Physical mixing is required to make a physical mixture. That is the way Applicants defined the phrase "physical mixture", and Applicants' definition excludes coatings because an enteric polymeric coating is not "physically mixed" with a drug in a core. In Bymaster, no mixing of a polymer with a solubility-improved drug form is disclosed otherwise, nor any corresponding physical mixture.

18. Bymaster makes no specific or general disclosure of a solubility-improved form of a drug within the scope of Applicants' claims in combination with a concentration-enhancing polymer, not even when disclosing embodiments of drugs in dosage forms having an enteric polymer coating. Even in the section (column 10, lines 57-67) where Bymaster mentions some of Applicants' polymers for use as enteric coatings, the only specific disclosure of a drug is of duloxetine and of "duloxetine-containing combinations". Duloxetine per se is not a salt, however, much less a solubility-improved drug form. Merck Index, Thirteenth Edition, Published by Merck Research Laboratories, page 611, entry 3498, copy previously supplied. In Bymaster's examples, there is no disclosure of any embodiment in which a solubility-improved drug form is physically mixed with a concentration-enhancing polymer required by Applicants' claims.

19. To repeat, per paragraph 1 above, an anticipation rejection requires the presence in a single prior art reference of each and every element of the claimed invention, arranged as in the claims. Anticipation cannot be based on picking and choosing from among unrelated portions of a disclosure to re-create a claimed invention. Here the Examiner has employed hindsight (i.e., the instant application) to choose a drug, choose a polymer, and then allege a physical mixture. But, such a physical mixture is nowhere disclosed in Bymaster. The anticipation rejection has no legal basis and Applicants accordingly submit that it should be withdrawn.

20. Applicants note that the §103 rejection over Bymaster set forth in the Office Action of March 13, 2006 was not repeated or continued in the present office action. Applicants acknowledge the withdrawal of the rejection with gratitude.

The §103(a) Obviousness Rejection Over Dunn

21. As a preliminary matter, Applicants' traversal of the rejection over Dunn assumes that the Examiner meant to include independent claim 86 within the scope of the rejection. Applicants' traversal below in respect of claim 86 should be taken as referring to independent claims 106 and 126 also.

22. It is well accepted that in order to establish a *prima facie* case of obviousness, an Examiner must satisfy three requirements: (1) there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine reference teachings; (2) the proposed modification of the prior art must have had a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the limitations of the claims. MPEP § 2142. In the instant rejection none of the three requirements has been satisfied.

23. The only drugs Dunn discloses within the scope of his disclosure are verapamil and verapamil hydrochloride, both drugs that are outside the scope of claim 86. Applicants' arguments from above supporting that these two species are outside Applicants' claims are incorporated by reference. Per the requirements for an obviousness rejection as set forth above from MPEP 2142 (1) Dunn is completely silent about the problem of increasing the concentration of a low-solubility drug, (2) there is no basis in Dunn which would lead one of ordinary skill to modify Dunn's teachings so as to co-administer a solubility-improved drug form and one of the required concentration-enhancing polymers and (3) Dunn does not teach the

combination of (a) co-administering (b) a solubility-improved drug form with (c) a cellulosic-ionizable concentration-enhancing polymer thereby (d) enhancing drug concentration by a factor of at least 1.25 relative to the equilibrium concentration. Indeed, element (b) is missing altogether. Dunn lacks any suggestion or motivation for modifying his teachings. Therefore, there can be no reasonable expectation of success.

24. Dunn is in fact concerned with the opposite problem to that solved by Applicants - - controlling the rate of solvation for a drug that is highly or moderately water soluble:

> For such products, controlling their rate of salvation after ingestion also influences their rate of absorption, and drugs which are highly or moderately water-soluble present special formulation problems. [Dunn, column 1, lines 16-19.]

and

> ...the present invention provides formulations which take into account the pH partition and which will release basic drugs into the small intestines at a constant and controlled rate, thereby controlling their serum level and prohibiting the peaks and valleys or erratic absorption which may be obtained with standard formulations. [Dunn, column 2, lines 57-63]

Clearly Dunn seeks to retard release rather than enhance concentration.

> The formulations of this invention retard the release of the active drug in the gastric juices where there is a low pH and subsequently there would be a high degree of nonionized material available, which would result in rapid absorption of the drug product. [Dunn, column 3, lines 41-45].

Dunn seeks to implement a constant order release rate and does so by retarding release, as opposed to Applicants who seek to enhance concentration. Dunn is unconcerned with the problem solved by Applicants, hence Dunn provides no basis for modifying his teachings in a way that would render Applicants obvious. Dunn is concerned with a wholly different problem (damping dissolution), in contrast to Applicants who seek to increase concentration by using a solubility-improved form and to generate an enhanced drug concentration by co-administering the solubility-improved drug form with a concentration-enhancing polymer.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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